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ICAM-3, a ligand for DC-SIGN, was duplicated from ICAM-1 in mammalian evolution, but was lost in the rodent genome

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Abstract ICAM-3 is a DC-SIGN ligand that is constitutively expressed on resting leukocytes, and is thus an important molecule for the first immune response. But, ICAM-3 has not been isolated form rodents. Thus, we compare the ICAM gene clusters in human, dog, mouse, and rat. ICAM-1, -4, -5 and -3 are located close to one another on the same chromosome and show genomic synteny in human and dog. Almost the same ICAM gene clusters were found in rodent genome, but only the ICAM-3 was not present. A phylogenetic tree plotting the cDNAs of human, dog, mouse, rat, and bovine suggested that ICAM-3 was made from a duplication of ICAM-1. Thus, ICAM-3 arose from ICAM-1 in the mammalian evolution, but was lost in the rodent's genome. Our study suggests the different immune response in the rodents in comparison with other mammals.

Keywords: ICAM-1; ICAM-3; DC-SIGN; Rodent's genome

1. Introduction

Approximately 3.5–5.0% of the human genome consists of highly conserved segmental duplicated regions [1]. These duplicated regions that include entire genes, allow gene diversification and/or the creation of novel functional roles for existing genes through selective constraints on one or more gene copies [2,3].

The ICAMs are type I membrane glycoproteins that are members of the Ig superfamily [4]. In mammals, five ICAMs, named ICAM-1 to -5, have been found [5–9]. Except for ICAM-5, all the ICAMs function in the immune system [4]. ICAM-5 is specifically expressed in neuronal cells of the telencephalon [10], but its function is still unclear.

ICAM-1 is expressed at low levels in resting leucocytes and at almost undetectable levels on the vascular endothelium and other cells [11]. However, ICAM-1 is rapidly upregulated by inflammatory cytokines such as interferon-α, interleukin 1-β, and tumor necrosis factor-α on many cell types, including leukocytes, endothelium, keratinocytes, epithelial cells, and fibroblasts [12]. These expression profiles indicate that ICAM-1 functions as a rapid-response molecule, present at low levels in resting states, but able to be induced rapidly in appropriate circumstances. In contrast, ICAM-3 is expressed at very high levels on all resting leukocytes; its expression is restricted to leukocytes and it does not have the broader expression profiles seen for other ICAMs. Moreover, the upregulation of ICAM-3 expression is induced only on leukocytes [7].

Both ICAM-1 and -3 bind integrin LFA1 [5,13], which is expressed at the surface of leukocytes. However, given their different expression profiles, these ICAMs must have very different functions. Thus, ICAM-3 is thought to be a key ligand for leukocyte LFA1 in initiating immune responses. ICAM-1's function could be initiated later, when the immune response is actively in progress.

For the first immune response, contact between dendritic cells (DC) and resting T-cells is essential. DCs are professional antigen-presenting cells that efficiently capture antigens to form an MHC-peptide complex [14–16]. How the initial contact between DCs and T cells, which is necessary for T-cell activation, is established and regulated has been largely unknown. The affinity of LFA1, which is expressed on DCs, for ICAM-3, even after integrin activation [17,18], is rather low [19,20], given that anti-LFA1 antibodies partially inhibit interactions between DCs and resting T-cells [21,22]. In 2000, a novel ICAM-3-binding C-type lectin named DC-SIGN, which is exclusively expressed by DCs, was shown to mediate strong adhesion between DCs and the ICAM-3 on resting T cells, and to be essential for the induction of T-cell proliferation [23]. Thus, ICAM-3 has a very important role in the primary immune systems.

Except for ICAM-2 [24], all the ICAMs are clustered within an 80-kb region on human chromosome 19p13.2 [25–27]. We compared the genomic region containing the ICAMs in human, dog, mouse, and rat. Our investigation found there was no ICAM-3 or ICAM-3-like sequence in mouse and rat. In contrast, human and dog had ICAM-3. Genomic PCRs revealed that all primates tested, from new world monkeys to the human, had ICAM-3. Bovine ICAM-3 has already been isolated [28].

Recent phylogenies of mammals place rodents and primates in the same clade exclusive of other mammals [29]. Thus, the ICAM-3 must have been duplicated from ICAM-1, but lost in the rodent lineages in the mammalian evolution.

2. Materials and methods

2.1. Sequence sources

The sequences of the human, dog, mouse, and rat ICAM genomic loci were taken from the public draft assemblies available at the UCSC genome browser (http://genome.ucsc.edu/) released May 2004 (human), July 2004 (dog), May 2004 (mouse), and June 2003 (rat). The following coordinates were used to obtain the human, dog, mouse, and rat sequences for Fig. 1: human chr19, 10231715-10322209; dog chr20, 53642218-53695917; mouse chr9, 21558757-21670259; rat chr8, 20031628-20128878.

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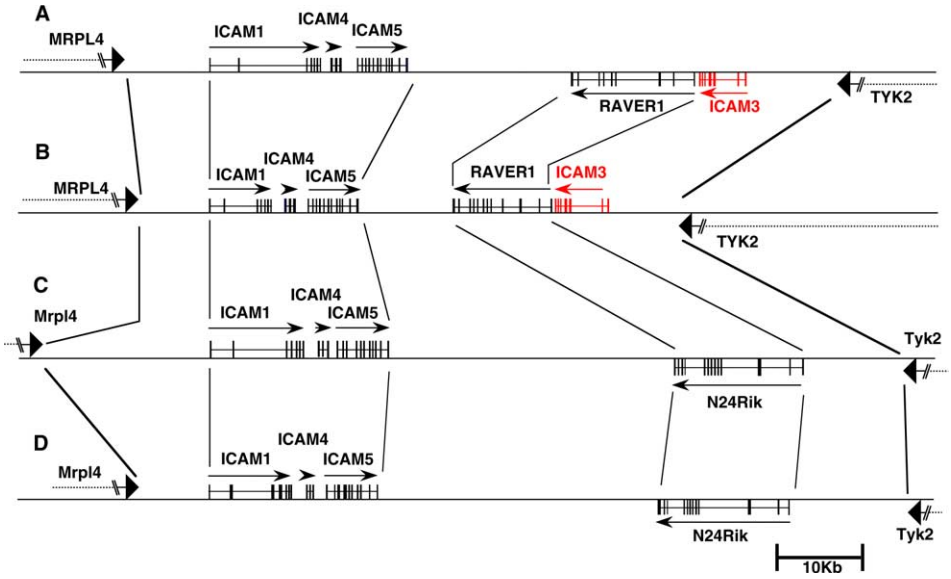

Fig. 1. Schematic representatations of the human (A), dog (B), mouse (C), and rat (D) ICAM gene clusters. Exons are shown as vertical black boxes. Bars connecting the genes of the four mammals indicate the corresponding genes and gene clusters. Arrows over the exons indicate their orientations on the chromosomes. In A and B, ICAM-3 is indicated in red.

2.2. Bioinformatics tools

Evolutionary tree: The cDNA sequences that encode the protein regions of all the ICAMs in the five mammals investigated were aligned by a multi-sequence Clustal X analysis (http://workshop.molecularevolution.org/software/clustalx/). Evolutionary trees were obtained by NJ analysis (1000 bootstraps). Comparisons of genomic regions: The genomic regions of ICAM-1 and -3, including the 10-kb upstream regions, were compared by the PipMaker program (http://pipmaker.bx.psu.edu/pipmaker/). The repeats were unmasked with the Repeat Masker program (http://www.repeatmasker.org/).

2.3. Genomic PCR

The human genomic DNAs were purchased from CLONTECH; chimpanzee, gorilla, and orangutan genomic DNAs were kindly provided by Drs. A. Fuijiyama and N. Sakaki (RIKEN); gibbon, Patas monkey, African green monkey, owl monkey, Pinche and ring-tailed lemur genomic DNAs were kindly provided by Dr. T. Ishida (University of Tokyo). The forward primer was designed for a consensus sequence in exon 1 of human RAVER1 and mouse and rat N24Rik (RAV-EX1: 5′-AGGCGTTTCCGGATCTCTTC-3′). The reverse primers were designed for the consensus sequences in exon 1 of human and dog ICAM-3 (I3-EX1-1, 5′-TGGGC GTGGTGACTATGC-3′; I3-EX1-2, 5′-CTGCTGGAGGGTCC-3′). For the bovine ICAM-3, the reverse primer was designed for exon 1 using the sequence in the public database (NM174349; I3-EX1-3, 5′-CACCCAGGGTCTACTGGACT-3′). The amplification was performed for 30 cycles; each cycle consisted of 20 s of denaturation at 98 °C and 10 min of annealing and elongation at 65 °C. LA-*Taq* polymerase (TAKARA) was used.

2.4. DNA sequencing of PCR products

The amplified PCR fragments were isolated from agarose gels using a QIAEXII gel extraction kit (QIAGEN), and direct sequencing using an ABI-3100 Genetic Analyzer (Applied Biosystems/Hitachi) was performed for the extracted DNAs.

3. Results

3.1. Comparison of the organization of human, dog, mouse, and rat ICAM gene clusters

To elucidate the evolutionary origins of ICAM gene clusters in mammals, we retrieved the genomic sequences of the human, dog, mouse, and rat ICAM gene clusters using the UCSC Genome Browser Home (http://genome.ucsc.edu/). In all four mammals, ICAM-1, -4, and -5 were located close to one another on the chromosome and showed genomic synteny (Fig. 1). These ICAMs were found between MRPL4 and tyrosine kinase 2 (TYK2). In all four mammals, RAVER1 (or N24Rik, the rodent counterpart of human RAVER1) lay between ICAM-5 and TYK2. Moreover, in the human and the dog we found an extra ICAM, ICAM-3 (Fig. 1A and B). The ICAM-3s were located between RAVER1 and TYK2, with the opposite orientation from ICAM-1, -4, and -5. In rodents, not even relic sequences of ICAM-3 were found between N24Rik and Tyk2 (Fig. 1C and D). Only ICAM-2 is located on another chromosome (human, chromosome 17; dog, chromosome 9; mouse, chromosome 11; and rat, chromosome 10), where it lies between SCN4A and ERN1 (data not shown).

3.2. ICAM-3 in other mammals

Next, to elucidate whether ICAM-3 existed in other mammals, we performed genomic PCR for primates, from new world monkeys to humans, and for bovine ICAM-3. However bovine ICAM-3 was already isolated [28], we performed the genomic PCR for the bovine to verify that ICAM-3 and RAVER1 were linked in bovine genome as they are in other mammals. The sense primer was located at the first exon of RAVER1 (Fig. 2A). The sequence of this primer was common to the human, mouse, and rat. Because the sequences of ICAM-3 are diversified in human and dog, we used three different reverse primers. Reverse primer 1 (ICAM-3-EX1-2) was used for the anthropoids (from the gibbon to the human). Reverse primer 2 (ICAM-3-EX1-2) was used for the other monkeys (from the Ring-tailed lemur to the Patas monkey). Reverse primer 3 (ICAM-3-EX1-3) was used for the bovine. In all primates and bovine, discrete bands of approximately 5.5–7.0 kb were amplified, and terminal sequence analysis of all the PCR products showed that they were all ICAM-3 and RAVER1. The sequence of the first exon and first intron of ICAM-3 of the Ring-tailed lemur and human have 92% simi-

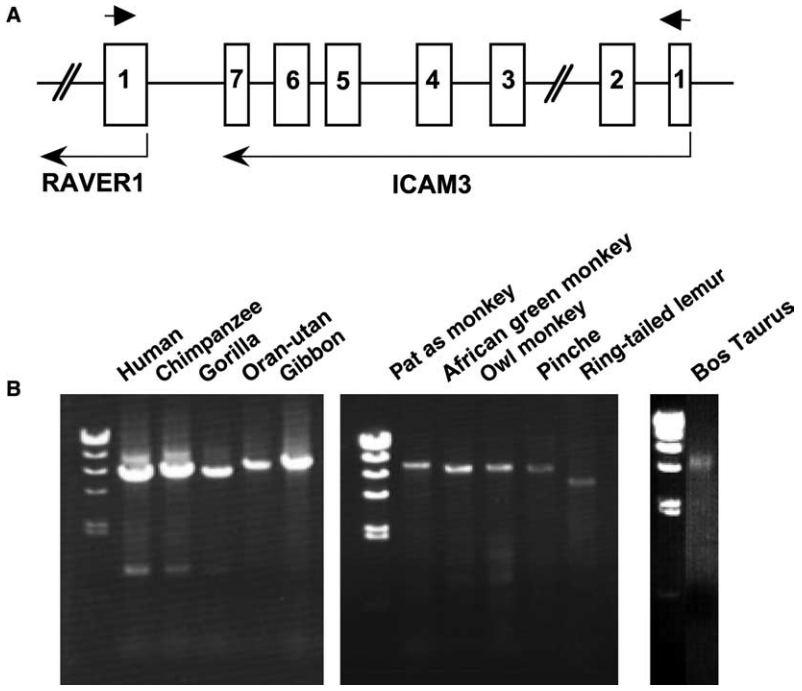

Fig. 2. Genomic PCRs of the sequence between RAVER1, exon 1 and ICAM-3, exon 1 for 10 primates and a bovine. A schematic representation of RAVER1 and ICAM-3 is shown in (A). The locations of the PCR primers are indicated above the exons. The 5.5–7.0-kb discrete bands (B) include ICAM-3.

larity (data not shown). Using these primers, we performed genomic PCR for four laboratory mouse strains (DBA2 C3H, BALB/c, 129) and three wild-type mouse strains (PGN2 (*M. m. domesticus*), BLG2 (*M. m. musculus*), and HMI (*M. m. castaneus*)), and failed to obtain any PCR products (data not shown).

3.3. The origin of ICAM-3

Comparison of the deduced primary amino acid domain structures of all human ICAMs showed that ICAM-1 and -3 have the same domain structures (Fig. 3A). The evolutionary relationships among all the ICAMs for human, dog, bovine, rat, and mouse is displayed in Fig. 3B. The phylogenetic tree shows that the ICAM-3s branched off from the ICAM-1s. Because rat and mouse split from one another 12 million years ago, and human and dog split approximately 65 million years ago, the evolutionary distance between the mouse and rat is much smaller than between human and dog. Compared with the other Ig-CAMs (NCAM1-, NCAM-2, L1CAM and MAG), the phylogenetic tree analysis shows that the ICAM family has diversified (data not shown). Among the ICAMs, the most closely related domain is the N-terminal one. There is a gradient of homology, with decreasing similarity toward the C-terminus. The LFA1-binding site has been mapped to domain 1, the functions of other domains have not been elucidated. The relative diversification of the ICAMs compared with the other Ig-CAMs may be a consequence of their bearing nonfunctional domains. In contrast, the NCAMs, L1CAM, and Mag bind homophilically, using all of their domains. Interestingly, between ICAM-1 and -3, there is a higher-than-expected homology between domain 2 and half of domain 3 [4]. So far, these domains have not been implicated in LFA1 engagement, so it is intriguing that they should remain so well conserved in an apparently nonfunctional area. This similarity in nonfunctional domains strongly suggests that ICAM-1 and -3 diversified recently, compared with the other ICAMs.

3.4. Comparison of the ICAM-1 and -3 genomic regions

Because ICAM-1 and -3 have opposite genomic orientations, we compared the complementary genomic sequence of ICAM-3 and the sense genomic sequence of ICAM-1 for human and dog. Both genomic sequences included approximately 10 kb of the 5′ upstream regions, which extend to the 3′ end of TYK2.

We performed this comparison using PipMaker (http://pipmaker.bx.psu.edu/pipmaker/) (Fig. 4). Exon 1 of both ICAM-1 and -3 contained a translation initiation methionine (ATG) followed by a putative signal peptide. Exons 2–6 encoded five individual Ig-like domains; these lie in the extracellular region. Exon 7 contained both the *trans*-membrane and cytoplasmic regions. In Fig. 4, A-1 shows human ICAM-1 vs. human ICAM-3; A-2 shows human ICAM-3 vs. human ICAM-1; B-1 shows dog ICAM-1 vs. dog ICAM-3; B-2 shows dog ICAM-3 vs. dog ICAM-1. Fig. 4A shows the highest similarities of exons 3–6 between human ICAM-1 and –3, respectively. Interestingly, human ICAM-1 and ICAM-3 share some homology in non coding DNA upstream of exon 3–7 and in the intron. Fig. 4B shows that exons 3–6 of the dog genomic ICAM-1 and -3 sequences are also conserved. Moreover, the relative positions of the ICAM-1 and -3 exons are similar. Exons 3–7 are closely clustered within about 2 kb. In contrast, exons 1 and 2 are located at a distance from the exon 3–7 cluster. These similarities of genomic sequence and exon location support the idea that a segmental duplication of ICAM-1 generated ICAM-3.

The regions surrounding the translation start site of human and dog ICAM-1 have a high CG content, which is depicted by

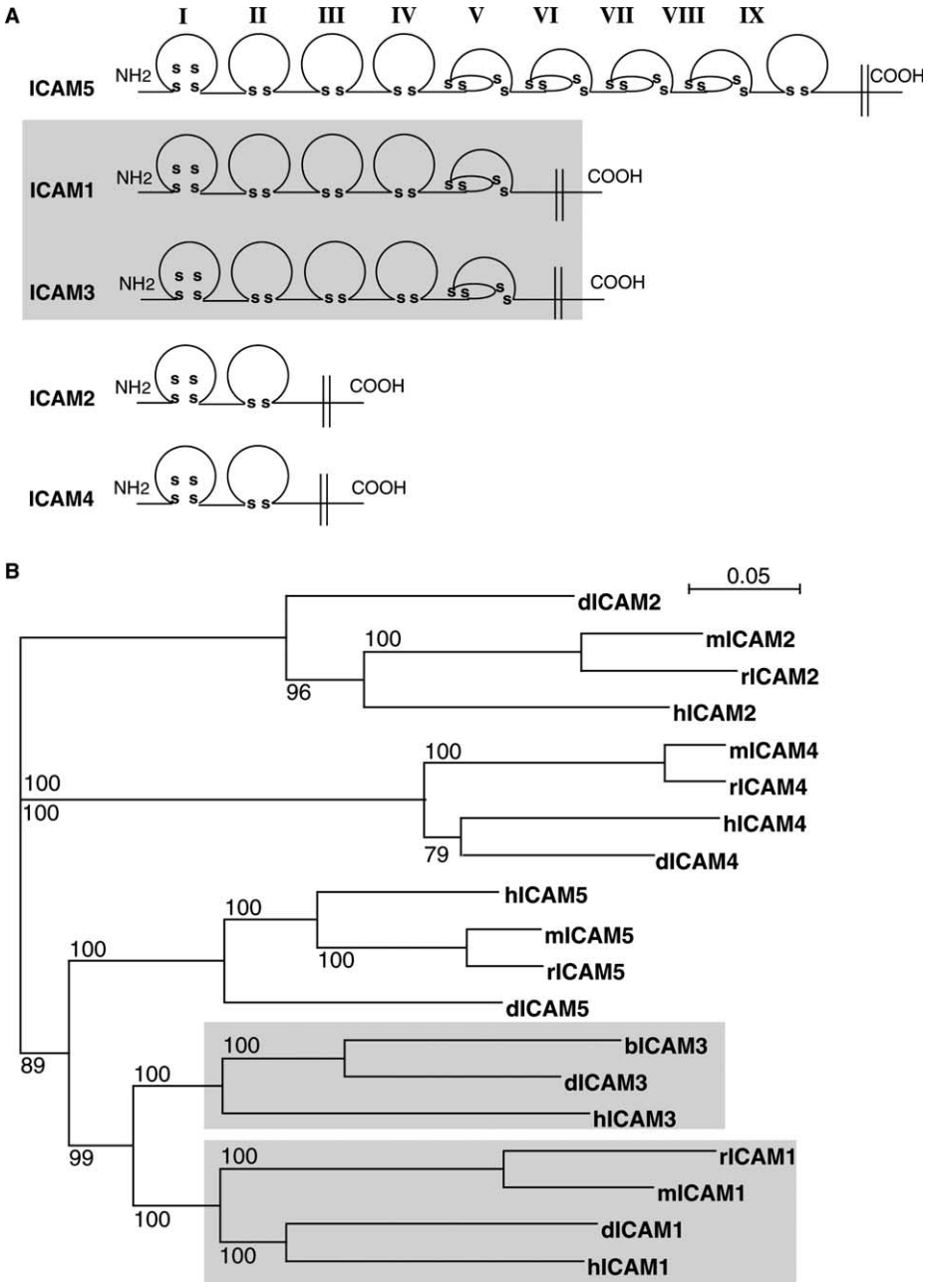

Fig. 3. (A) Proposed model of the domain structures of human ICAMs 1–5. Individual Ig-like domains are numbered I-IX above. The extra- and intracellular orientations are indicated by the NH_2 and COOH at the ends of the protein chains. SS represents intrachain disulfide bonds. The two short parallel lines denote the plasma membrane. ICAM-s 1and 3 are shaded. (B) Phylogenetic tree of human, dog, mouse, rat, and bovine ICAMs (hICAM, human ICAM; dIICAM, dog ICAM; mICAM, mouse ICAM; rICAM, rat ICAM; bICAM, bovine ICAM). The phylogenetic tree was created using cDNA sequences of protein-encoding regions. The numbers shown on the labeled branches are percentages that were calculated from 1000 bootstrap replicates. The scale bar equals a distance of 0.05.

a gray rectangle in Fig. 4A-1 and B-1. These CG islands are lost in human ICAM-3 and significantly decreased in dog ICAM-3. During the evolutionary period following the duplication of ICAM-1, the 5-methylated Cs were deaminated and converted to T residues.

4. Discussion

It has long been claimed that ICAM-3 and -1 are more closely related to each other than either is to other ICAMs [4]. In this report, we obtained strong evidence that ICAM-3 was generated by the segmental duplication of ICAM-1 in the mammalian evolution. In non-rodent animals, the segment corresponding to the one between rodent Mrp14 and ICAM-4 was duplicated and lies in the region between RAVER1 (the rodent N24Rik counterpart) and TYK2 in the reverse orientation to the other ICAMs (Fig. 1). The comparative analysis of the genomic region of ICAM-1 and -3 in human and dog revealed a similar exon organization and high Pip ratio, including in the intronic region. These similarities support the idea that ICAM-3 originated as a duplication of ICAM-1.

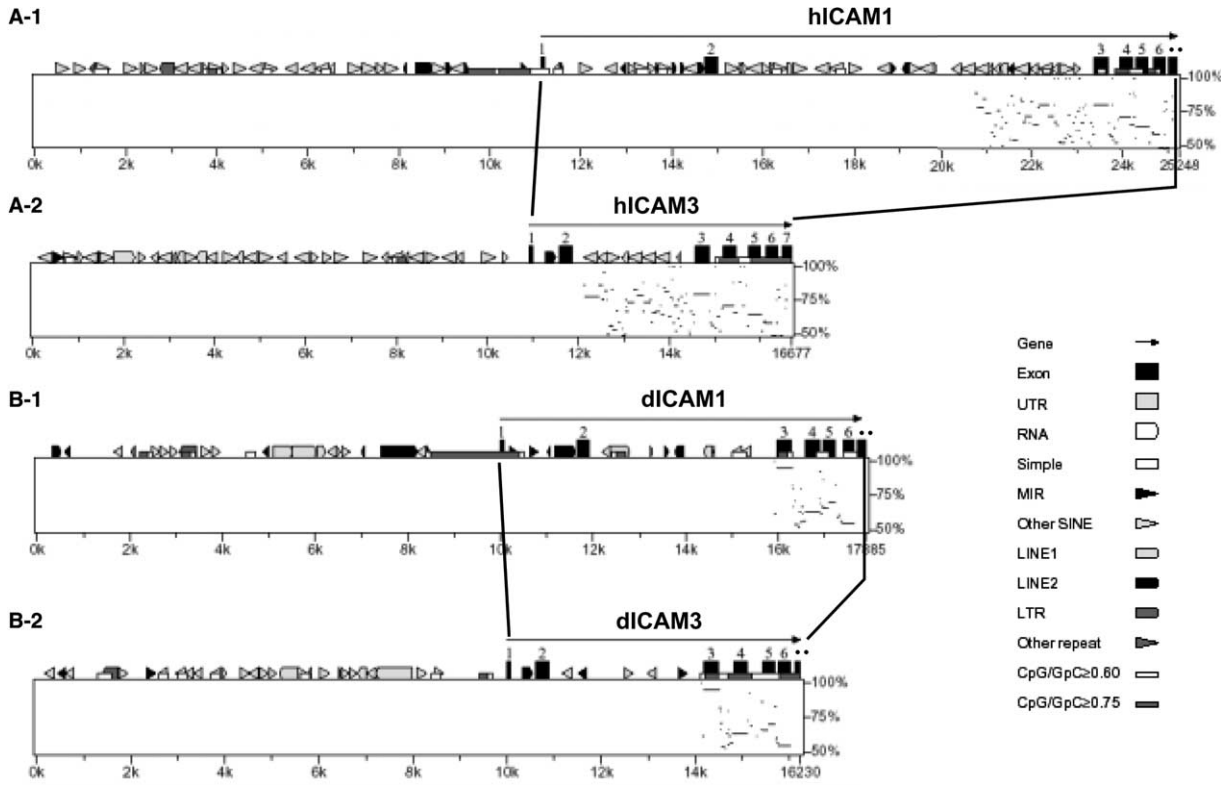

Fig. 4. PipMaker plot of the regions surrounding the genomic regions of ICAM-s 1 and 3 with unmasked repeats. (A-1) Human ICAM-1 versus human ICAM-3. (A-2) Human ICAM-3 versus human ICAM-1. (B-1) Dog ICAM-1 versus dog ICAM-3. (B-2) Dog ICAM-3 versus dog ICAM-1. The corresponding regions of ICAM-s 1 and 3 are indicated by black bars.

In contrast, rodents (mouse and rat) have no ICAM-3 (Fig. 1). Thus, we could set up two hypotheses. First, the duplication that generated ICAM-3 from ICAM-1 was not ancestral to the rodent lineage. Second, ICAM-3 was already duplicated from ICAM-1 and present in the common ancestor of rodents as well as other mammals, but only in the rodents, ICAM-3 was lost in their genome. Recently, mammalians phylogenies have placed rodents and primates in the same clade exclusive of other mammals [29]. In fact, based on rather extensive published molecular data, rodent and primate are more closely related to each other than either group is to carnivores (dog) [29–33]. This strongly implies that ICAM-3 was already present in common ancestor of mammalians. Therefore, more likely explanation is that ICAM-3 was lost in the rodent lineage by a deletion event. In support of a deletion being the cause, evidence suggest that small-scale genomic DNA deletion have played a significant role in reducing the DNA content of rodent genome [34] and this has resulted in loss of some gene present in other mammals [35]. This is a simple and likely explanation for the deletion of ICAM-3 in rodents.

ICAM-3 is constitutively expressed, mainly on resting leukocytes, and binds to DCs, which present MHC-antigen peptides through a C-type lectin named DC-SIGN [23]. Thus, ICAM-3 is a key molecule for the primary immune response. In this report, we show that mouse and rat do not have ICAM-3. However, mouse DC-SIGN [36] has been found. The amino acid sequence similarity between the carbohydrate recognition domain of human DC-SIGN and mouse DC-SIGN is 69% [36]. Thus, in rodents, instead of ICAM-3, ICAM-2 or some other Ig family member that is expressed on resting leukocytes may bind to DC-SIGN.

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